Claims

1 A method for determining the stage of neurofibrillary degeneration associated with a tauopathy in a subject believed to suffer from the disease, which method comprises the steps of:
(i) introducing into the subject a ligand capable of labelling aggregated paired helical filament (PHF) tau protein,
(ii) determining the presence and\or amount of ligand bound to extracellular aggregated PHF tau in the medial temporal lobe of the brain of the subject,
(iii) correlating the result of the determination made in (ii) with the extent of neurofibrillary degeneration in the subject.

2 A method as claimed in claim 1 wherein the determination in step (ii) is used to establish the density ligand binding.

3 A method as claimed in claim 1 or claim 2 wherein the correlation in step (iii) is made by reference to historical data.

4 A method as claimed in any one of the preceding claims wherein the tauopathy is Alzheimer Disease (AD).

5 A method as claimed in claim 4 wherein the extent of neurofibrillary degeneration is related to the neuropathological staging of the progression of AD according to the defined hierarchical system shown in Figure 2c.

6 A method as claimed in any one of the preceding claims wherein the ligand is capable of crossing the blood brain barrier.

7 a method as claimed in any one of the preceding claims wherein the ligand is conjugated, chelated, or otherwise associated, with a detectable chemical group.

8 A method as claimed in claim 7 wherein the ligand is labelled for SPECT and is not capable taken up intracellularly.

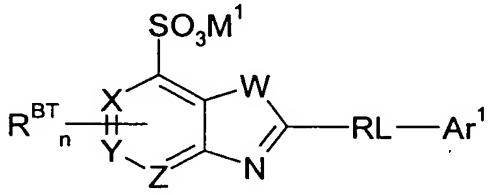
9 A method as claimed in claim 8 wherein a ligand comprises a

technetium-chelating group.

10 A method as claimed in claim 7 wherein the ligand is labelled for positron emission tomography (PET).

11 A method as claimed in claim 10 wherein the ligand comprises a positron-emitting carbon, optionally incorporated into a methyl group present in the ligand.

12 A method as claimed in any one of the preceding claims wherein the ligand is a compound of the formula:



wherein:

W is S, O, or NH;

exactly one of X, Y, and Z is CH or N;

the others of X, Y, and Z are CH;

M^1 is an alkali metal cation selected from: Li, Na, K, or Cs.

RL is a rigid linker group;

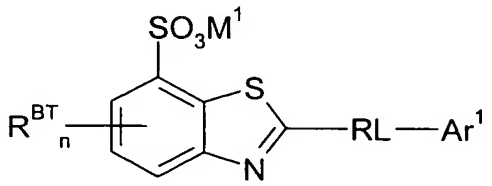
Ar^1 is an C_{5-20}aryl group;

n is an integer from 0 to 3; and,

each R^{BT} is independently a core substituent.

13 A method as claimed in claim 12 wherein each of X, Y, and Z is CH.

14 A method as claimed in claim 13 wherein the ligand is a compound of the formula:



wherein:

M^1 is an alkali metal cation selected from: Li, Na, K, or Cs.

RL is a rigid linker group;
Ar^1 is an C_{5-20}aryl group;
n is an integer from 0 to 3; and,
each R^{BT} is independently a benzothiazole substituent.

15 A method as claimed in any one of claims 12 to 14 wherein each of the rigid linker group, RL, and the aryl group, Ar^1, are substantially planar.

16 A method as claimed in any one of claims 12 to 15 wherein the rigid linker group, RL, and the aryl group, Ar^1, together with the core group, form a compound which is substantially planar.

17 A method as claimed in any one of claims 12 to 16 wherein the twist is no greater than that of the compound of Figure 16.

18 A method as claimed in any one of claims 12 to 17 wherein the compound has a compound length which is from about 14.7 AU to about 15.3 AU.

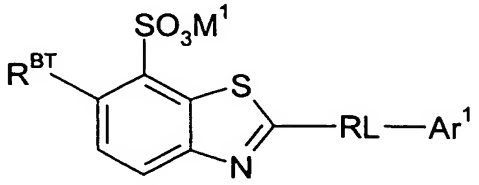
19 A method as claimed in any one of claims 12 to 18 wherein each R^{BT} is independently C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, nitro, cyano, halo, or amino.

20 A method as claimed in claim 19 wherein each R^{BT} is independently -Me, -Et, -nPr, -iPr, -OH, -OMe, -OEt, -O(nPr), -O(iPr), $-NO_2$, -CN, -F, -Cl, -Br, -I, $-NH_2$, $-NH_2$, -NHMe, -NHEt, -NH(iPr), -NH(nPr), $-NMe_2$, $-NEt_2$, $N(iPr)_2$, or $-N(nPr)_2$.

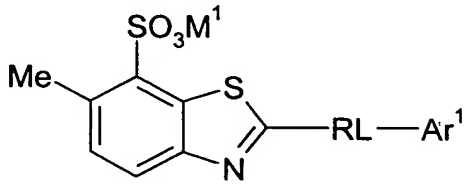
21 A method as claimed in claims 19 wherein each R^{BT} is independently C_{1-4}alkyl.

22 A method as claimed in any one of claims 19 to 21 wherein n is 1, and R^{BT} is independently -Me, -Et, -nPr, or -iPr.

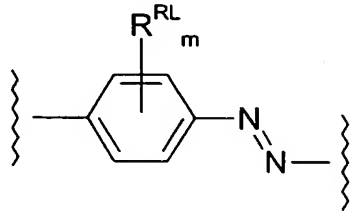
23 A method as claimed in any one of claims 12 to 22 wherein the ligand has the following formula:



24 A method as claimed in claim 23 wherein the ligand has the following formula:



25 A method as claimed in any one of claims 12 to 24 wherein RL is a group of the formula:

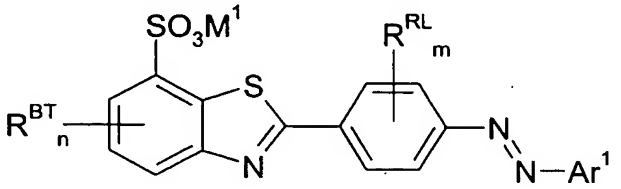


wherein:

m is an integer from 0 to 4, and

each R^{RL} is independently a rigid linker aryl substituent,

and the ligand has the formula:



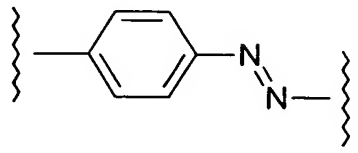
26 A method as claimed in claim 25 wherein each R^{RL} is independently C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, nitro, cyano, halo, or amino.

27 A method as claimed in claim 26 wherein each R^{RL} is independently -Me, -Et, -nPr, -iPr, -OH, -OMe, -OEt, -O(nPr),

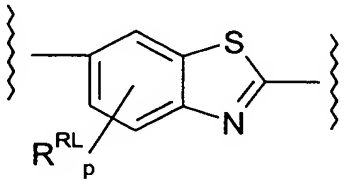
-O(iPr), $-NO_2$, -CN, -F, -Cl, -Br, -I, $-NH_2$, $-NH_2$, -NHMe, -NHEt, -NH(iPr), -NH(nPr), $-NMe_2$, $-NEt_2$, $N(iPr)_2$, or $-N(nPr)_2$.

28 A method as claimed in claim 26 wherein each R^{RL} is independently C_{1-4}alkyl.

29 A method as claimed in any one of claims 1 to 24 wherein RL is a group of the formula:



30 A method as claimed in any one of claims 1 to 24 wherein RL is a group of the formula:

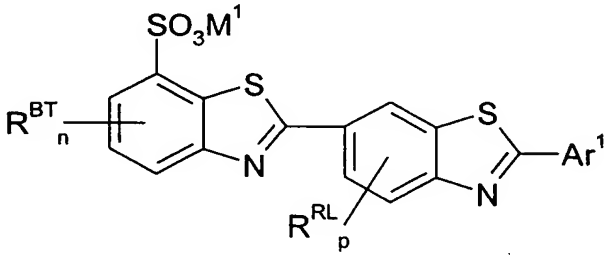


wherein

p is an integer from 0 to 3, and

each R^{RL} is independently a rigid linker aryl substituent,

and the compounds have the formula:

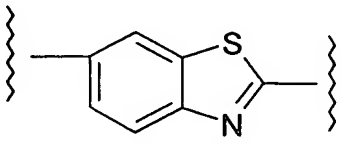


31 A method as claimed in claim 30 wherein each R^{RL} is independently C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, nitro, cyano, halo, or amino.

32 A method as claimed in claim 31 wherein each R^{RL} is independently -Me, -Et, -nPr, -iPr, -OH, -OMe, -OEt, -O(nPr), -O(iPr), $-NO_2$, -CN, -F, -Cl, -Br, -I, $-NH_2$, $-NH_2$, -NHMe, -NHEt, -NH(iPr), -NH(nPr), $-NMe_2$, $-NEt_2$, $N(iPr)_2$, or $-N(nPr)_2$.

33 A method as claimed in claim 31 wherein each R^{RL} is independently C_{1-4} alkyl.

34 A method as claimed in any one of claims 12 to 24 and 30 to 33 wherein RL is a group of the formula:



35 A method as claimed in any one of claims 12 to 34 wherein Ar^1 is selected from groups derived from benzene (C_6), naphthalene (C_{10}), anthracene (C_{14}), phenanthrene (C_{14}), naphthacene (C_{18}), and pyrene (C_{16}).

36 A method as claimed in any one of claims 12 to 34 wherein Ar^1 is selected from:

C_5heteroaryl groups derived from furan (oxole), thiophene (thiole), pyrrole (azole), imidazole (1,3-diazole), pyrazole (1,2-diazole), triazole, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, and oxatriazole; and

C_6heteroaryl groups derived from isoxazine, pyridine (azine), pyridazine (1,2-diazine), pyrimidine (1,3-diazine), pyrazine (1,4-diazine), triazine, tetrazole, and oxadiazole (furazan).

37 A method as claimed in any one of claims 12 to 34 wherein Ar^1 is selected from:

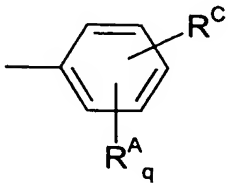
C_9heterocyclic groups derived from benzofuran, isobenzofuran, indole, isoindole, purine, benzimidazole;

C_{10}heterocyclic groups derived from quinoline, isoquinoline, benzodiazine, pyridopyridine, quinoxaline;

C_{13}heterocyclic groups derived from carbazole; and,

C_{14}heterocyclic groups derived from acridine, xanthene, phenoxathiin, phenazine, phenoxazine, phenothiazine.

38 A method as claimed in claim 35 wherein Ar^1 is an aryl group having a phenyl core, and has the formula:



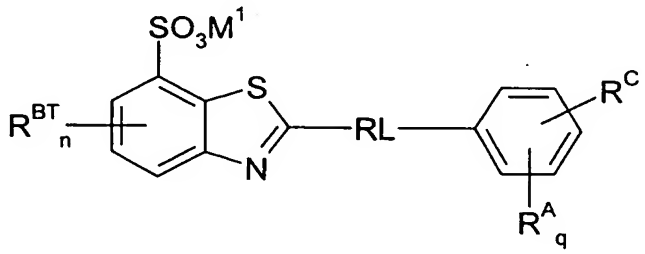
wherein

q is an integer from 0 to 5; and

each R^A is independently an aryl substituent;

R^C, if present, is a reactive conjugating substituent, or R^C is, or contains, a detectable label;

and the compound has the formula:



39 A method as claimed in claim 38 wherein R^C is present and is a reactive conjugating substituent, and is, or contains, a reactive functional group suitable for conjugation to another molecule by chemical reaction therewith, to form a covalent linkage therebetween.

40 A method as claimed in claim 39 wherein R^C is present and is, or contains, an active ester.

41 A method as claimed in claim 40 wherein R^C is present and is, or contains, a succinimidyl ester.

42 A method as claimed in claim 39 wherein R^C is present and is a reactive conjugating substituent, and is, or contains, a moiety suitable for conjugation to another molecule by a strong non-covalent interaction.

43 A method as claimed in claim 42 wherein R^C is present and is, or contains, biotin.

44 A method as claimed in claim 39 wherein R^C is present and is a reactive conjugating substituent, and is, or contains, a moiety suitable for conjugation to another molecule by complex or chelate formation.

45 A method as claimed in claim 44 wherein R^C is present and is, or contains, a technetium-chelating group.

46 A method as claimed in claim 45 wherein R^C is present and is, or contains diethylenetriaminepentaacetic acid.

47 A method as claimed in claim 38 wherein R^C is present and is, or contains, a detectable label.

48 A method as claimed in claim 47 wherein R^C is present and is, or contains, a dye, a fluorescent marker, an antigenic group, a stable or an unstable isotope, or a positron-emitting carbon atom.

49 A method as claimed in claim 48 wherein R^C is present and is, or contains, ^{18}F.

50 A method as claimed in claim 48 wherein R^C is present and is, or contains, a positron-emitting carbon atom.

51 A method as claimed in any one of claims 38 to 50 wherein each R^A is independently selected from:

$-OH$, $-NH_2$, $-NHR^1$, $-NR^1R^2$, $-SO_3M^2$, and C_{1-4}alkyl;

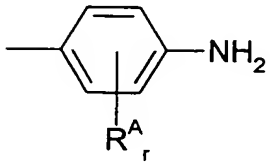
wherein:

R^1 and R^2 are each C_{1-4}alkyl, and

M^2 is an alkali metal cation selected from Li, Na, K, or Cs.

52 A method as claimed in claim 51 wherein at least one R^A is $-OH$ or $-NH_2$.

53 A method as claimed in claim 52 wherein Ar^1 is an aryl group having an amino-substituted phenyl core, and has the formula:



wherein

r is an integer from 0 to 4,

and each R^A is independently an aryl substituent.

54 A method as claimed claim 53 wherein each R^A is independently selected from:

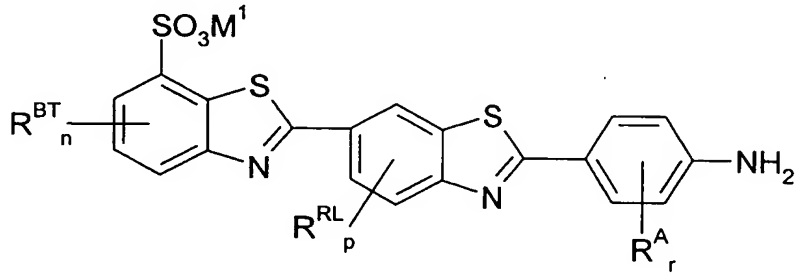
-OH, $-NH_2$, $-NHR^1$, $-NR^1R^2$, $-SO_3M^2$, and C_{1-4}alkyl;

wherein:

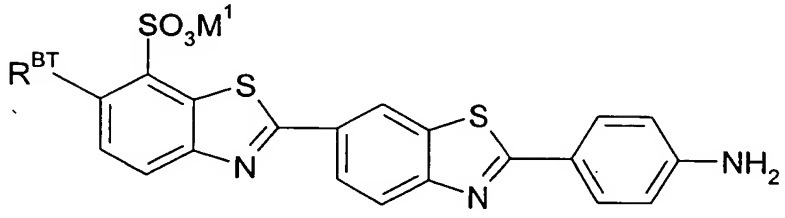
R^1 and R^2 are each C_{1-4}alkyl, and

M^2 is an alkali metal cation seleted from Li, Na, K, or Cs.

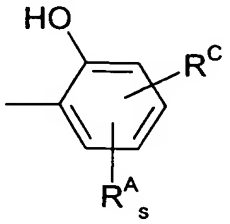
55 A method as claimed in claim 54 wherein the ligand has the formula:



56 A method as claimed in claim 55 wherein the ligand has the formula:



57 A method as claimed in claim 52 wherein Ar^1 is an aryl group having a hydroxy-substituted phenyl core, and has the formula:

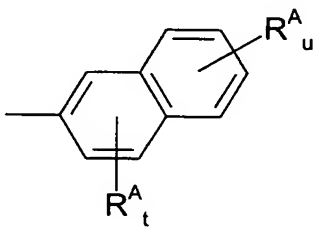


wherein

s is an integer from 0 to 4, and
each R^A is independently an aryl substituent, and
R^C, if present, is a reactive conjugating substituent, or
R^C is, or contains, a detectable label.

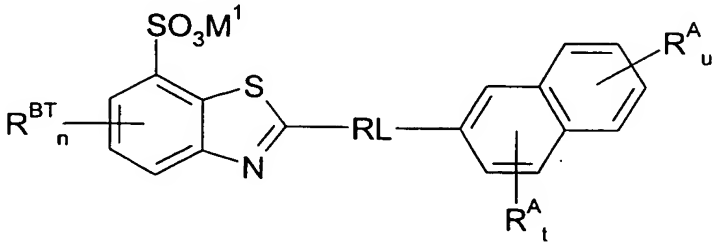
58 A method as claimed in claim 57 wherein the ligand is as defined in any one of claims 108 to 150.

59 A method as claimed in claim 35 wherein Ar^1 is an aryl group having a naphthyl core, and has the formula:

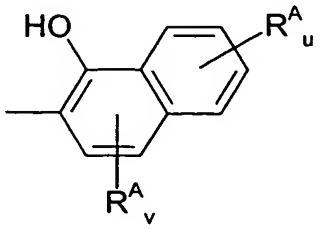


wherein

t is an integer from 0 to 3,
u is an integer from 0 to 4, and
each R^A is independently an aryl substituent,
and the compound has the formula:



60 A method as claimed in claim 59 wherein Ar^1 is an aryl group having a hydroxy-substituted naphthyl core, and has the formula:



wherein

v is an integer from 0 to 2,

u is an integer from 0 to 4, and

each R^A is independently an aryl substituent.

61 A method as claimed in claim 59 or claim 60 wherein each R^A is independently selected from:

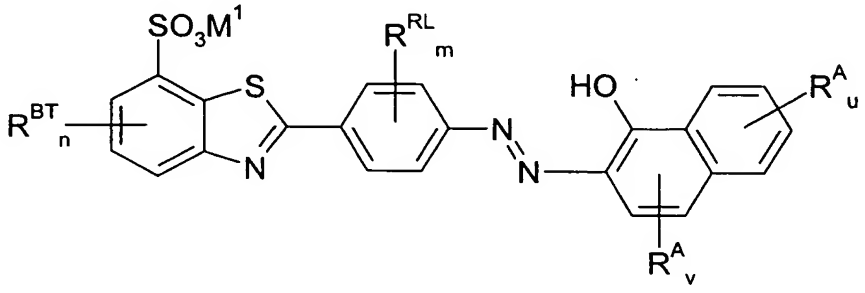
-OH, $-NH_2$, $-NHR^1$, $-NR^1R^2$, $-SO_3M^2$, and C_{1-4}alkyl;

wherein:

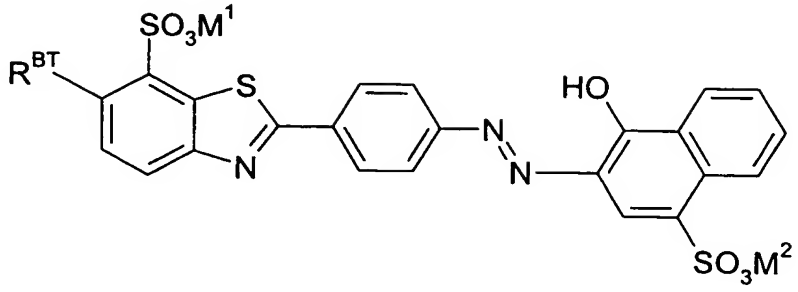
R^1 and R^2 are each C_{1-4}alkyl, and

M^2 is an alkali metal cation selected from: Li, Na, K, or Cs.

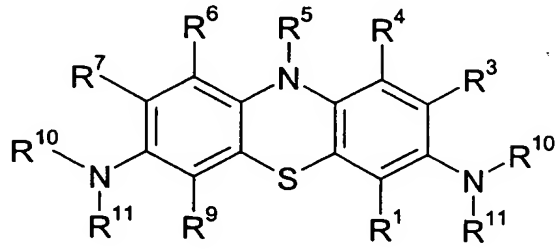
62 A method as claimed in claim 61 wherein the ligand has the formula:



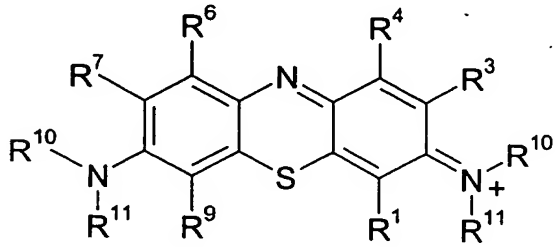
63 A method as claimed in claim 62 wherein the ligand has the formula:



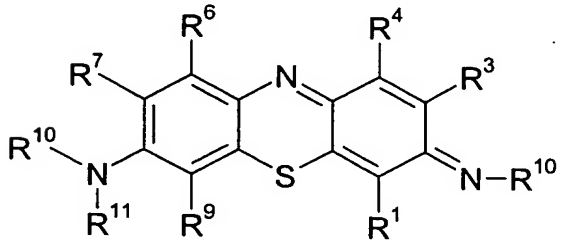
64 A method as claimed in any one of claims 1 to 11 wherein the ligand is a compound of one of the following formulae:



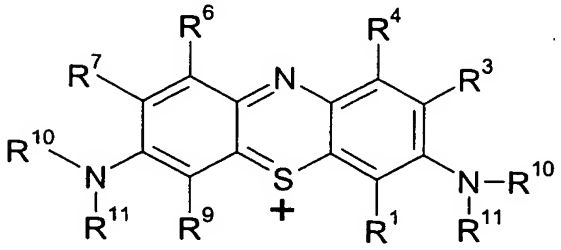
(I)



(II)



(III)



(IV)

wherein:

each of R_1, R_3, R_4, R_6, R_7 and R_9 is independently hydrogen,

halogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

R_5 is independently hydrogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

R_{10} and R_{11} are independently selected from hydrogen, hydroxy, carboxy, substituted or unsubstituted alkyl, haloalkyl, or alkoxy;

or a pharmaceutically acceptable salt thereof.

65 A method as claimed in claim 64 wherein:

each of R_1, R_3, R_4, R_6, R_7 and R_9 is independently hydrogen, halogen, hydroxy, carboxy, substituted or unsubstituted C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkoxy;

R_5 is independently hydrogen, hydroxy, carboxy, substituted or unsubstituted C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkoxy;

R_{10} and R_{11} are independently selected from hydrogen, hydroxy, carboxy, substituted or unsubstituted C_{1-6}alkyl, C_{1-4}haloalkyl, or C_{1-6}alkoxy.

66 A method as claimed in claim 65 wherein said C_{1-6}alkyl is selected from: methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, and isohexyl.

67 A method as claimed in claim 65 or claim 66 wherein the substituents of said substituted C_{1-6}alkyl are selected from: mercapto, thioether, nitro, amino, aryloxy, halogen, hydroxyl, carbonyl, C_{5-20}aryl, C_{1-6}cycloalkyl, and non-aryl C_{3-20}heterocyclyl.

68 A method as claimed in any one of claims 65 to 67 wherein said C_{1-4}haloalkyl is selected from: chloromethyl, 2-bromethyl, 1-chloroisopropyl, 3-fluoropropyl, 2,3-dibrombutyl, 3-chloroisobutyl, iodo-t-butyl, and trifluoromethyl.

69 A method as claimed in any one of claims 64 to 68 wherein the ligand is an acid addition salt formed between a compound described in said claims and an acid.

70 A method as claimed in claim 69 wherein the acid is an inorganic acid or an organic acid.

71 A method as claimed in claim 70 wherein the ligand is a chloride salt.

72 A method as claimed in claim 70 wherein said organic acid is selected from: acetic acid, citric acid, maleic acid, fumaric acid, tartaric acid, methanesulphonic acid, and p-toluenesulphonic acid.

73 A method as claimed in any one of claims 64 to 72 wherein:

R_1, R_3, R_4, R_6, R_7 and R_9 are independently -H, $-CH_3$, $-C_2H_5$, or $-C_3H_7$;

R_{10} and R_{11} are independently -H, $-CH_3$, $-C_2H_5$ or $-C_3H_7$;

R_5 is independently -H, $-CH_3$, $-C_2H_5$, or $-C_3H_7$.

74 A method as claimed in claim 73 wherein the ligand is shown in Figure 8b.

75 A method as claimed in any one of claims 64 to 74 wherein the ligand comprises a positron-emitting carbon.

76 A method as claimed in any one of the preceding claims wherein (ii) further comprises the step of additionally determining the presence and\or amount of a ligand bound to intracellular aggregated tau in a neocortical structure of the brain of the subject.

77 A method as claimed in claim 76 wherein the ligand used to bind to extracellular aggregated PHF tau in the medial temporal lobe and the ligand used to bind to intracellular aggregated PHF tau in the neocortical structure of the brain are labelled distinctively.

78 A method as claimed in claim 76 or claim 77 wherein the ligand used to bind intracellular aggregated tau is the ligand described in any one of claims 64 to 75.

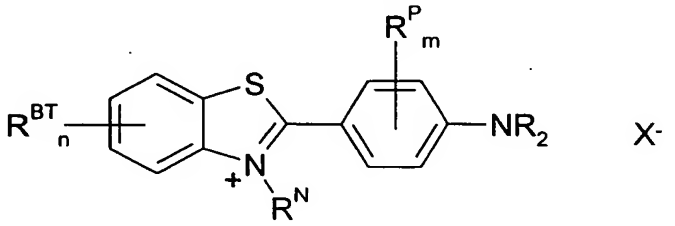
79 A method as claimed in any one of the preceding claims wherein

the ligand binds aggregated PHF tau preferentially with respect to competing binding sites present in the relevant region of the brain.

80 A method as claimed in any one of the preceding claims wherein steps (i) and\or (ii) of the method are performed in conjunction with the further step of introducing into the subject a further blocking ligand which labels the competing binding sites present in the relevant region of the brain preferentially to the ligand used to bind aggregated PHF tau.

81 A method as claimed in claim 80 wherein the blocking ligand is [^{18}F]FDDNP.

82 A method as claimed in claim 80 wherein the blocking ligand is a benzthiazole of the formula:



wherein:

n is an integer from 0 to 4;

each R^{BT} is independently a blocking ligand benzothiazole substituent;

m is an integer from 0 to 4;

each R^{P} is independently a phenylene substituent;

each R is independently -H or an amino substituent; and,

either:

R^{N} and X^{-} are both absent and the associated (tertiary) nitrogen atom is neutral;

or:

R^{N} is a benzothiazolino substituent and the associated (quaternary) nitrogen atom bears a positive charge, and X^{-} is a counter ion.

83 A method as claimed in claim 82 wherein the blocking ligand is thioflavin-T.

84 A method as claimed in claim 82 wherein each R^{BT}, is independently C_{1-4}alkyl, $-SO_3H$, or $-SO_3M^3$, wherein M^3 is a cation.

85 A method as claimed in claim 84 wherein M^3 is an alkali metal cation selected from: Li, Na, K, or Cs.

86 A method as claimed in any one of claims 82 to 85 wherein n is 1, and R^{BT} is -Me, -Et, -nPr, or -iPr.

87 A method as claimed in claim 86 wherein n is 1, and R^{BT} is -Me.

88 A method as claimed in claim 84 wherein one of the R^{BT} groups is $-SO_3H$ or $-SO_3M^3$, and another of the R^{BT} groups is C_{1-4}alkyl.

89 A method as claimed in any one of claims 82 to 85 wherein n is 2, and one R^{BT} is C_{1-4}alkyl, and one R^{BT} is $-SO_3H$ or $-SO_3M^3$.

90 A method as claimed in claim 89 wherein n is 2, and one R^{BT} is -Me, and one R^{BT} is $-SO_3H$ or $-SO_3M^3$.

91 A method as claimed in any one of claims 82 to 90 wherein R^N and X^- are both absent and the associated (tertiary) nitrogen atom is neutral.

92 A method as claimed in any one of claims 82 to 90 wherein R^N is a benzothiazolino substituent and the associated (quaternary) nitrogen atom bears a positive charge, and X^- is a counter ion.

93 A method as claimed in any one of claims 82 to 90 wherein R^N is C_{1-4} alkyl.

94 A method as claimed in claim 93 wherein R^N is -Me, -Et, -nPr, or -iPr.

95 A method as claimed in any one of claims 82 to 90 wherein X^- is Cl^-, Br^-, and I^-.

96 A method as claimed in any one of claims 82 to 95 wherein R^P is

C_{1-4}alkyl.

97 A method as claimed in any one of claims 82 to 96 wherein each R is -H, and the amino group is $-NH_2$.

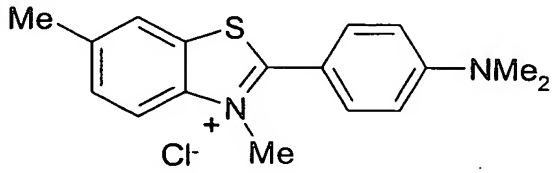
98 A method as claimed in any one of claims 82 to 96 wherein one R is -H and one R is an amino substituent.

99 A method as claimed in any one of claims 82 to 96 wherein each R is an amino substituent.

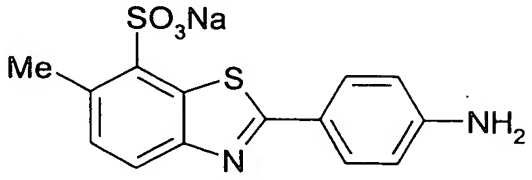
100 A method as claimed in claim 99 wherein each of the amino substituents is C_{1-4}alkyl.

101 A method as claimed in any one of claims 82 to 96 wherein the amino group, $-NR_2$, is $-NH_2$, -NHMe, -NHEt, -NH(iPr), -NH(nPr), $-NMe_2$, $-NEt_2$, $N(iPr)_2$, or $-N(nPr)_2$.

102 A method as claimed in claim 101 wherein the blocking ligand is a benzthiazole of the formula:



103 A method as claimed in claim 101 wherein the blocking ligand is a benzthiazole of the formula:



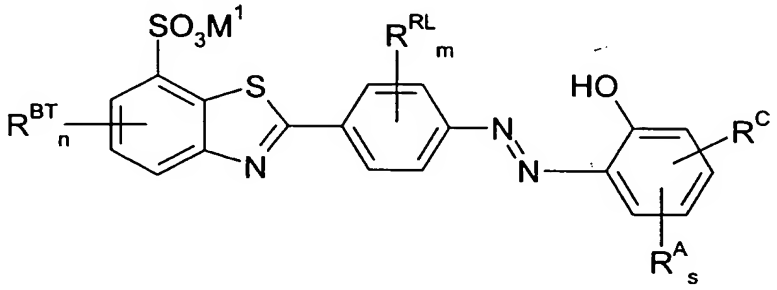
104 A method as claimed in any one of the preceding claims for use in the diagnosis or prognosis of a tauopathy in a subject believed to suffer from said disease.

105 A method as claimed in claim 104 wherein tauopathy is AD.

106 A ligand as described in any one of claims 1 to 79 for use in a method of diagnosis or prognosis of a tauopathy in a subject believed to suffer from said disease, said method being a method as described in claim 104 or claim 105.

107 A ligand as described in any one of claims 1 to 79 for use in a method for determinining the effectiveness of a treatment of a subject with a tau-tau aggregation inhibitor to inhibit neurofibrillary degeneration in that subject, the method comprising use of a method as described in any one of claims 1 to 103.

108 A ligand of the formula:



wherein:

M^1 is an alkali metal cation;

n is an integer from 0 to 3;

each R^{BT} is a independently benzothiazole substituent;

m is an integer from 0 to 4;

each R^{RL} is independently a rigid linker aryl substituent;

s is an integer from 0 to 4;

each R^A is independently an aryl substituent; and,

R^C, if present, is a reactive conjugating substituent, or R^C is, or contains, a detectable label.

109 A ligand as claimed in claim 108 wherein M^1 is Li, Na, K, or Cs.

110 A ligand as claimed in claim 108 or claim 109 wherein each R^{BT} is independently C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, nitro, cyano, halo, or amino.

111 A ligand as claimed in claim 110 wherein each R^{BT} is independently -Me, -Et, -nPr, -iPr, -OH, -OMe, -OEt, -O(nPr), -O(iPr), $-NO_2$, -CN, -F, -Cl, -Br, -I, $-NH_2$, $-NH_2$, -NHMe, -NHEt, -NH(iPr), -NH(nPr), $-NMe_2$, $-NEt_2$, $N(iPr)_2$, or $-N(nPr)_2$.

112 A ligand as claimed in claim 110 wherein each R^{BT} is independently C_{1-4}alkyl.

113 A ligand as claimed in claim 112 wherein each R^{BT} is independently -Me, -Et, -nPr, or -iPr.

114 A ligand as claimed in claim 113 wherein each R^{BT} is -Me.

115 A ligand as claimed in claim 113 wherein n is 1, and R^{BT} is independently -Me, -Et, -nPr, or -iPr.

116 A ligand as claimed in claim 115 wherein n is 1, and R^{BT} is -Me.

117 A ligand as claimed in any one of claims 108 to 116 wherein the benzothiazole group has the following formula:

118 A ligand as claimed in claim 117 wherein the ligand has the following formula:

119 A ligand as claimed in any one of claims 108 to 118 wherein each R^{RL} is independently C_{1-4}alkyl, hydroxy, C_{1-4}alkoxy, nitro, cyano, halo, or amino.

120 A ligand as claimed in claim 119 wherein each R^{RL} is independently -Me, -Et, -nPr, -iPr, -OH, -OMe, -OEt, -O(nPr), -O(iPr), $-NO_2$, -CN, -F, -Cl, -Br, -I, $-NH_2$, $-NH_2$, -NHMe, -NHEt, -NH(iPr), -NH(nPr), $-NMe_2$, $-NEt_2$, $N(iPr)_2$, or $-N(nPr)_2$.

121 A ligand as claimed in claim 120 wherein each R^{RL} is independently C_{1-4}alkyl.

122 A ligand as claimed in any one of claims 108 to 121 wherein each R^A is independently selected from:

-OH, $-NH_2$, $-NHR^1$, $-NR^1R^2$, $-SO_3M^2$, and C_{1-4}alkyl;

wherein:

R^1 and R^2 are each C_{1-4}alkyl, and

M^2 is an alkali metal cation.

123 A ligand as claimed in claim 122 wherein M^2 is Li, Na, K, or Cs.

124 A ligand as claimed in any one of claims 108 to 123 wherein R^C is present and is a reactive conjugating substituent, and is, or contains, a reactive functional group suitable for conjugation to another molecule by chemical reaction therewith, to form a covalent linkage therebetween.

125 A ligand as claimed in claim 124 wherein R^C is present and is, or contains, an active ester.

126 A ligand as claimed in claim 125 wherein R^C is present and is, or contains, a succinimidyl ester.

127 A ligand as claimed in claim 124 wherein R^C is present and is a reactive conjugating substituent, and is, or contains, a moiety suitable for conjugation to another molecule by a strong non-covalent interaction.

128 A ligand as claimed in claim 127 wherein R^C is present and is, or contains, biotin.

129 A ligand as claimed in claim 124 wherein R^C is present and is a reactive conjugating substituent, and is, or contains, a moiety suitable for conjugation to another molecule by complex or chelate formation.

130 A ligand as claimed in claim 129 wherein R^C is present and is, or contains, a technetium-chelating group.

131 A ligand as claimed in claim 130 wherein R^C is present and is, or contains diethylenetriaminepentaacetic acid.

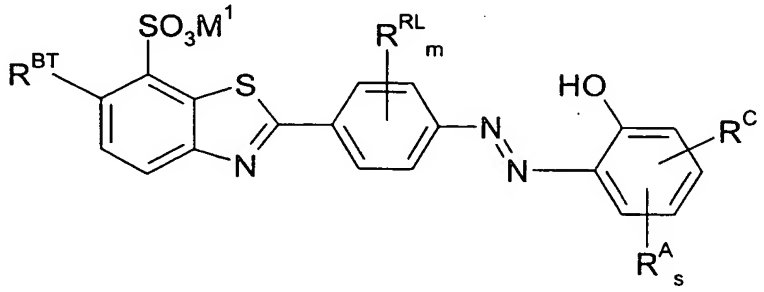
132 A ligand as claimed in any one of claims 108 to 123 wherein R^C is present and is, or contains, a detectable label.

133 A ligand as claimed in claim 132 wherein R^C is present and is, or contains, a dye, a fluorescent marker, an antigenic group, a stable or an unstable isotope, or a positron-emitting carbon atom.

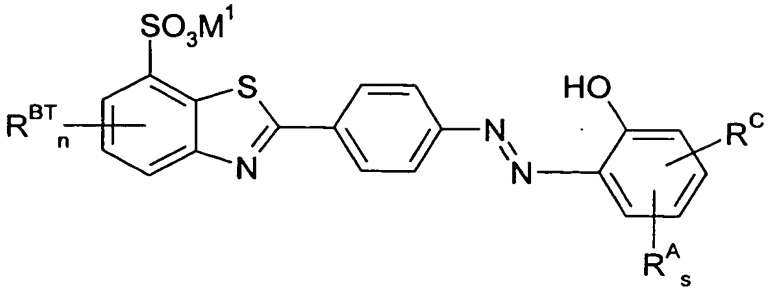
134 A ligand as claimed in claim 133 wherein R^C is present and is, or contains, ^{18}F.

135 A ligand as claimed in claim 134 wherein R^C is present and is, or contains, a positron-emitting carbon atom.

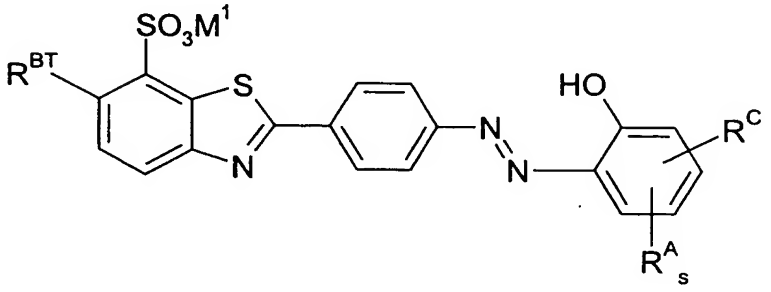
136 A ligand as claimed in any one of claims 108 to 135 wherein the ligand has the formula:



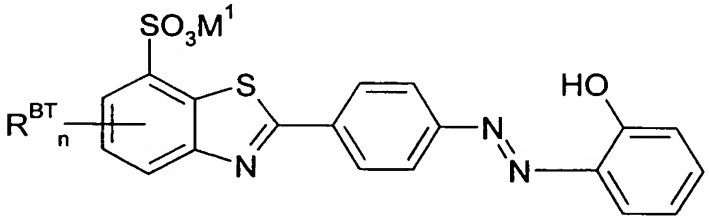
137 A ligand as claimed in claim 136 wherein the ligand has the formula:



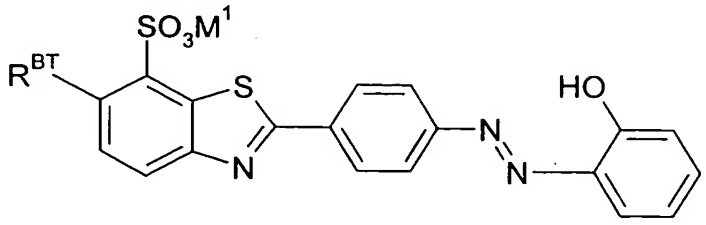
138 A ligand as claimed in claim 137 wherein the ligand has the formula:



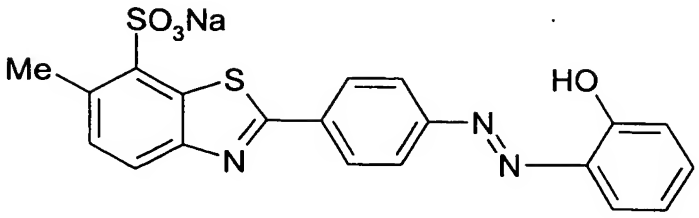
139 A ligand as claimed in claim 137 wherein the ligand has the formula:



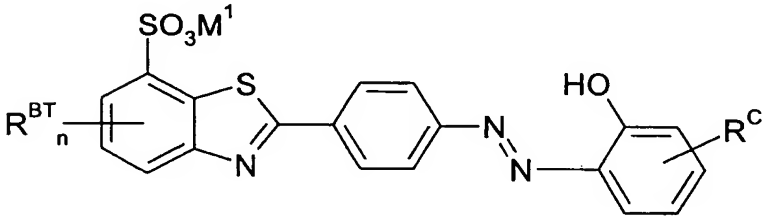
140 A ligand as claimed in claim 139 wherein the ligand has the formula:



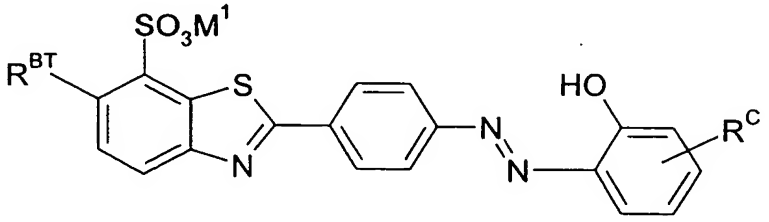
141 A ligand as claimed in claim 140 wherein the ligand has the formula:



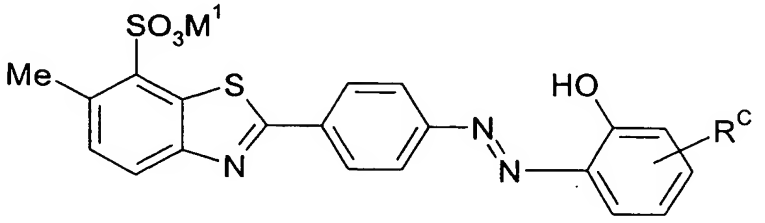
142 A ligand as claimed in claim 137 wherein the ligand has the formula:



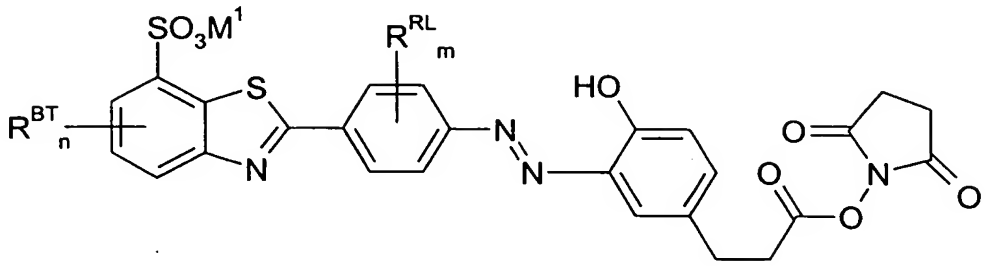
143 A ligand as claimed in claim 142 wherein the ligand has the formula:



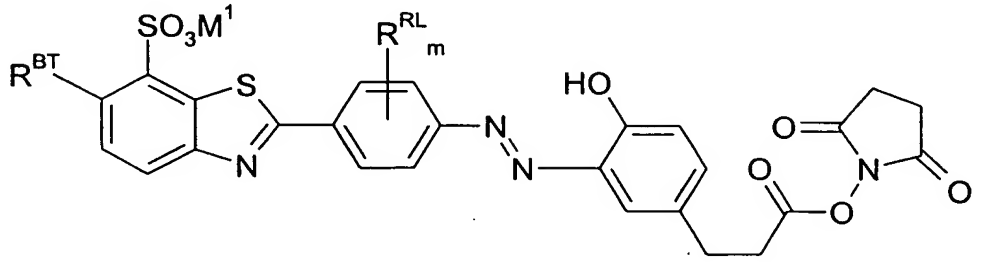
144 A ligand as claimed in claim 143 wherein the ligand has the formula:



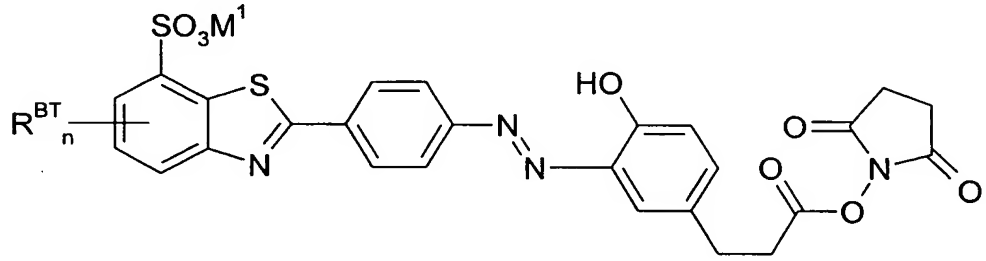
145 A ligand as claimed in claim 142 wherein the ligand has the formula:



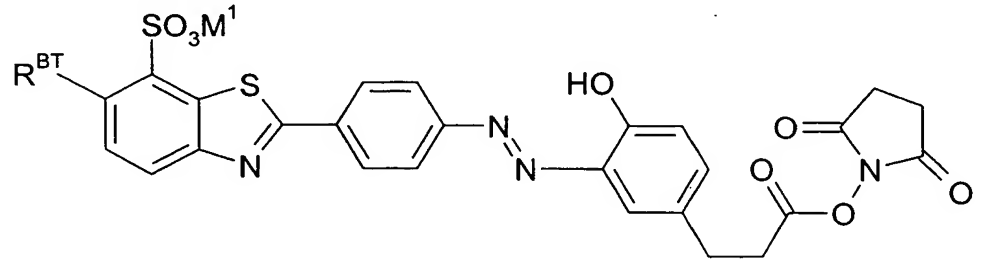
146 A ligand as claimed in claim 145 wherein the ligand has the formula:



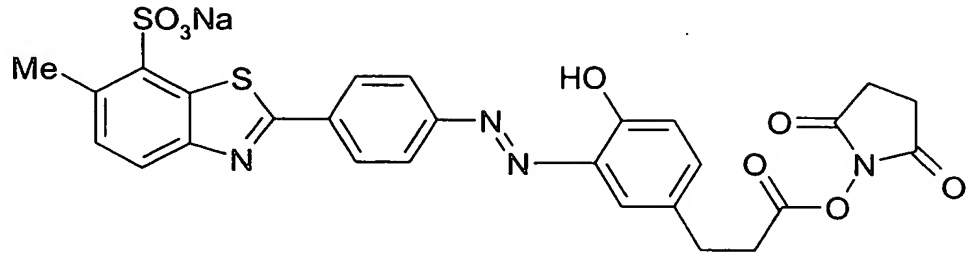
147 A ligand as claimed in claim 145 wherein the ligand has the formula:



148 A ligand as claimed in any one of claim 147 wherein the ligand has the formula:



149 A ligand as claimed in claim 148 wherein the ligand has the formula:



150 A ligand as claimed in any one of claims 136 to 149 which is conjugated, chelated, or otherwise associated, with a detectable chemical group.

151 A diagnostic composition comprising as its active ingredient at least 90%, 95%, or 98% of the ligand of any one of claims 108 to 150.

152 A diagnostic composition as claimed in claim 151 further comprising a carrier material or other pharmaceutically- and physiologically-acceptable excipient.

153 A method of labelling aggregated tau or tau-like molecules, comprising contacting the aggregated molecules with a ligand or composition of any one of claims 108 to 152.

154 An *in vitro* method of diagnosis or prognosis of a tauopathy in a subject believed to suffer from the disease, the method comprising (i) obtaining a sample of appropriate tissue from a subject; (ii) contacting the sample with a ligand or composition of any one of claims 108 to 152; (iii) detecting the amount and\or localisation of the ligand bound to the sample (iv) correlating the result of (iii) with the stage or severity of the disease in the subject.

155 A method as claimed in claim 153 where the tauopathy is AD.

156 A ligand according to any one of claims 108 to 150 for use in a method of diagnosis, prognosis or therapeutic treatment of the

human or animal body for a tauopathy.

157 A ligand as claimed in claim 156 where the tauopathy is AD.

158 A method for identifying a compound capable of binding aggregated tau protein, the method comprising the steps:
(i) providing a sample of aggregated tau protein to which a ligand as claimed in any one of claims 108 to 150 has been bound,
(ii) contacting the sample with the putative tau-binding compound,
(iii) determining the extent of displacement of the ligand from the aggregated tau protein by the putative tau-binding compound
(iv) correlating the result of the determination made in (iii) with the ability of the compound to bind aggregated tau protein.

159 A method as claimed in claim 158 wherein the aggregated tau protein is in solution or bound to a solid phase.

160 An *in vitro* method for identifying a ligand capable of labeling aggregated PHF tau protein, the method comprising the steps of:
(i) providing a first agent suspected of being capable of labeling aggregated PHF tau protein,
(ii) contacting (a) a tau protein or a derivative thereof containing the tau core fragment bound to a solid phase so as to expose a high affinity tau capture site, with (b) a liquid phase tau protein or derivative thereof capable of binding to the solid phase tau protein or derivative, and (c) said selected first agent and (d) a second agent known to be tau-tau binding inhibitor,
(iii) selecting first agent which fully or partially relieves the inhibition of binding of the liquid phase tau protein or derivative of (b) to the solid phase tau protein or derivative of (a) by the inhibitor (d).

161 A method as claimed in claim 160 wherein step (ii) is carried out in conjunction with:
(i*bis*) contacting (a) a tau protein or a derivative thereof containing the tau core fragment bound to a solid phase so as to expose a high affinity tau capture site, with (b) a liquid phase

tau protein or derivative thereof capable of binding to the solid phase tau protein or derivative, and (c) said first agent, and (*ibis*.1) detecting inhibition of tau-tau binding as exhibited by inhibition of binding of the liquid phase tau protein or derivative of (b) to the solid phase tau protein or derivative of (a), (*ibis*.2) selecting first agent which has minimal or absent activity as tau-tau binding inhibitors and\or optionally enhance tau-tau binding.

162 A method as claimed in claim 160 or claim 161 wherein the inhibitor is a diaminophenathiozine as described in any one of claims 64 to 74.

163 A method as claimed in claim 162 wherein the inhibitor is DMMB.

164 A method as claimed in any one of claims 160 to 163 wherein the liquid phase tau protein or derivative is prepared in a form which has undergone partial aggregation prior to exposure to the solid phase.

165 A method as claimed in claim 174 wherein said preparation of liquid phase tau protein or derivative comprises the steps of:
(i) sonicating said tau protein or derivative and\or
(ii) exposing said tau protein or derivative to PEG through a semi-permeable membrane.

166 A method as claimed in any one of claims 160 to 165, wherein the step of contacting said agent and liquid phase tau protein or derivative with said solid phase tau protein or derivative is carried out in an alkaline buffer of pH 9-10.

167 A method as claimed in any one of claims 160 to 165, wherein the step of contacting said agent and liquid phase tau protein or derivative with said solid phase tau protein or derivative is carried out in physiological buffer conditions.

168 A method as claimed in any one of claims 160 to 165, wherein the step of contacting the or each agent and liquid phase tau protein or derivative with said solid phase tau protein or derivative is carried out in 50-400 mM sodium chloride or a salt or salt mixture of comparable ionic strength, and in a pH range of 4-10.

169 A method as claimed in any one of claims 160 to 168, wherein said liquid phase tau protein or derivative is labeled.

170 A method as claimed in any one of claims 160 to 168 wherein said liquid phase tau protein or derivative is immunologically distinguishable from said solid phase tau protein or derivative, and the binding is detected by antibodies.

171 A method as claimed in any one of claims 160 to 170 wherein a truncated tau protein corresponding to the core fragment and terminating at Ala390 (dGA) is plated on a solid phase in buffer conditions unfavourable to tau-tau association,

172 A method as claimed in any one of claims 160 to 171 wherein a truncated tau protein corresponding to the core fragment and terminating at Glue-391 (dGAE) or a full-length protein is added in liquid phase together with the or each agent

173 A method as claimed in any one of claims 158 to 172 further comprising the step of formulating the agent as a diagnostic or prognostic reagent.

174 A method as claimed in any one of claims 158 to 172 further comprising the step of using the agent as a ligand in the method of any one of claims 1 to 11.